LOCHT et al
Serial No. 08/765,287
January 23, 2004

REMARKS/ARGUMENTS

Entry of the foregoing and favorable reconsideration and reexamination of the subject application, as amended, pursuant to and consistent with 37 C.F.R. Section 1.112, and in light of the remarks which follow, are respectfully requested.

By the present amendment, claims 1 to 15, 18 to 22, 27 to 30, 34, 35, 37, 38 and 40 have been amended to place the claims in proper U.S. format. Support for the promoter in Claim 1 appears at least on page 8, paragraph 5, referring to minor adjustments when the construct is expressed in other gram negative bacteria; at least on page 9, paragraph 4, where it is stated that the recombinant DNA is under the control of a "suitable promoter" and in Claim 12 as originally filed. Support for the term translational is inherent in the constructs in the Examples and more specifically Examples 4 and 5 of the specification as filed. Applicants submit that no new matter has been added.

Furthermore, the amended claims in which the term "translational" has been inserted is an inherent feature of the recombinant DNA that is claimed. Therefore, Applicants submit that insertion of this term is not new matter and permissible under law. See, *Westvaco Corp. v. International Paper Co.*, 23 USPQ 1401, 1424 (E.D. Va 1991) *aff'd*, 991 F2d 735, 26 USPQ2d 1353 (Fed. Cir. 1993) where the court allowed an amendment since:

> The matters purported to be new were merely express descriptions of functions or properties inherent in the original patent disclosure.

Prior to specifically addressing the issues brought to bear by the Examiner in the Official Action, Applicants would like to briefly discuss the present invention. The presented invention relates to recombinant DNA encoding an immunogenic fusion protein, this recombinant DNA comprises a sequence (1) coding for a polypeptide heterologous with respect to a filamentous hemagglutinin of *Bordetella* (Fha) fused in the same reading frame with **a sequence (2) placed upstream from said sequence (1)**, said sequence (2) coding for at least a part of the precursor of the Fha, this part comprising the site of interaction of the Fha with heparin, said sequence (2) being placed under the control of a promoter and when introduced into a cell culture is expressed in said cell culture or exposed at the surface of cells, wherein said recombinant DNA is expressed as an immunogenic **translational fusion protein**.

The Examiner will notice that Applicants have highlighted the parts of the above paragraph, which is a reiteration of Claim 1, that distinguish the present invention from the cited prior art. It should be clear that two sequences coding for a polypeptide and at least part of the precursor are fused in the same reading frame such that expression is achieved of an immunogenic translational fusion protein **are two different sequences which are expressed together in the recombinant DNA**. Thus, the recombinant DNA of the present invention links two different sequences **that code** for two different proteins, which Applicants submit is neither taught nor suggested in the cited prior references. This will be clearly demonstrated below.

Turning now to the Official Action, Claims 1 to 15, 18 to 22, 27 to 30 and 39 have been rejected under 35 U.S.C. §103 (a) as obvious over Loosmore et al in view of Menozzi et al. For the following reasons, this rejection is respectfully traversed.

In rendering this rejection, the Examiner purports that Loosmore et al teach Fhap/TOX, Fhap/PRN and TOXp/Fha constructs, which the Examiner believes are hybrid constructs which qualify as the fusion agent and the gene product expressed by Loosemore's pertussis structural gene qualifies as a polypeptide heterologous with respect to Fha of *Bordetella*. The Examiner further relies on Menozzi et al to conclude that the FHA described in Loosmore et al has a heparin interaction site.

First of all Loosmore et al fail to describe a translational fusion protein. Rather they describe a transcriptional fusion protein. The differences between translational and transcriptional fusion proteins are set forth in Exhibit 1. Furthermore, Loosmore et al fails to suggest or even disclose the production of a translational fusion protein in which two different sequences one coding for a heterologous polypeptide and the other coding for at least a part of the precursor of the Fha are fused in the same reading frame and expressed as fusion proteins.

Rather, Loosmore et al disclose a promoter (which is not a sequence that codes for a polypeptide and is therefore not expressed) fused to a TOX or PRN or Fha sequence. Thus in Loosmore et al only one sequence is present in their recombinant DNA constructs that encodes a sole polypeptide.

Moreover, Loosmore et al describe at column 1 that the purpose of producing their particular recombinant DNA constructs was either to optimize antigen production

which may either increase or decrease the yield of the antigens produced. In the case of FHA production, it is taught at column 5, lines 23 to 31 that using the TOX promoter linked to a FHA that the amount of FHA was significantly reduced 50 to 100-fold.

Thus, it should be clear that only a single antigen *per se* is present in the recombinant DNA constructs described in Loosemore et al and a translational fusion protein is neither generated nor expressed.

Furthemore, it should be noted that Loosmore et al describes that the genes for FHA used in their recombinant constructs are those described in Rehlman et al and Relman et al describes using a *B. pertussis* strain BP536.

Menozzi et al describe the purification of *Bordetella pertussis* hemagglutinin using heparin affinity chromatography. This reference fails to describe where the heparin binding site is located on the FHA. Indeed, FHA is described as having a molecular mass of 220 kDA (approximately 10,000 nucleic acids), which is a very large protein. Furthermore, the experiments in Menozzi used two streptomycin resistant strains of *B. pertussis* Tohame I and *B. pertussis* BPRA, which are different strains than those described in Loosmore et al.

Therefore, a person skilled in the art would not know with certainty whether the FHA described in Loosmore et al would contain a heparin binding site as described in Menozzi et al since the heparin site was not identified and the sources of the FHA are in fact different.

Even if the Examiner comes to a different conclusion concerning the heparin binding site of Loosmore et al, the combination of Loosmore t al with Menozzi et al

would not render the presently claimed invention obvious since both references are silent with respect to describing a recombinant DNA that expresses a translational fusion protein having a heparin binding site, in which two different sequences are present in the recombinant DNA construct and are expressed together as a translational fusion protein.

Moreover, Loosmore et al does not suggest to alter their recombinant DNA in any manner. This is not surprising since the purpose of Loosmore et al's invention was to increase or decrease the expression of various antigens of *B. pertussis* in a recombinant construct which would produce strains that would be more economical by altering the natural promoter sequences. Thus, there was no suggestion to alter the coding sequences of Fha to produce a translational fusion protein.

As stated by the Federal Circuit in *Sibia Neurosciences Inc. V. Cadus Pharmaceutical Corp.* 55 USPQ2d 1927 (Fed. Cir. 2000):

> To establish a prima facie case of obviousness, the prior art reference (or references when combined) must teach or suggest all the claim limitations MPEP§ 2142. In addition, if a reference needs to be modified to achieve the claimed invention **"there must be a showing of a suggestion or motivation to modify the teachings of that reference** to the claimed invention in order to support the obviousness conclusion (emphasis added)

Since no such suggestion of modification is described in either of the cited prior art references of Loosmore et al and Menozzi et al, this rejection cannot be maintained.

Therefore, in view of the above, withdrawal of this rejection is respectfully requested.

Claims 34, 35 and 37 have been rejected under 35 U.S.C. § 103(a) as being obvious over Loosmore et al in view of Menozzi et al and Locht et al. For the following reasons, this rejection is respectfully traversed.

Loosmore et al and Menozzi et al have been discussed extensively above with respect to the obviousness rejection. The same arguments are incorporated herein for this rejection. It should be recalled that neither Loosmore et al nor Menozzi et al suggest a recombinant DNA a sequence (1) coding for a polypeptide heterologous with respect to a filamentous hemmagglutinin of *Bordetella* (Fha) fused in the same reading frame with a sequence (2) placed upstream from said sequence (1), said sequence (2) coding for at least a part of the precursor of the Fha, this part comprising at least the N-terminal region of a truncated mature Fha protein which contains the site of interaction of the Fha with heparin, whereupon expression a translational fusion protein is obtained.

The reference of Locht et al does not remedy the deficiencies of the primary reference. Locht et al does not suggest a recombinant DNA as presently set forth in Claim 34. Furthermore, this reference is a review article concerning FHA produced by *Bordetella* spp. The Examiner cites Locht et al as describing the immunogeneicity of FHA when presented to the mucosal immune system and concludes that it would be obvious to a person skilled in the art to use the recombinant construct taught by Loosmore et al modified with the FHA having a heparin binding site decribed by Menozzi et al for administration to the mucosal system.

However, Locht et al do not disclose that the N-terminal part of the FHA molecule can in fact elicit protective immunity. This is clear from at least page 659, column 1 first

full paragraph of this reference. Nor does Locht et al provide any teaching of how to design a recombinant construct using FHA that may confer protective immunity by mucosal administration.

The combination of these references fails to render the present claims of this rejection obvious since none of these references teach or even suggest the recombinant DNA as presently set forth in Claim 34 having two different sequences fused together and expressing a translational fusion protein.

As stated in *In re Burt and Walter*, 148 USPQ 549 (CCPA 1966):

> [S]ilence in a reference is not a proper substitute for an adequate disclosure of facts from which a conclusion of obviousness may justifiably follow.

The lack of any suggestion to modify recombinant DNA of Loosmore et al or to express two sequences as a fusion protein renders Claims 34, 35 and 37 unobvious over the cited prior art.

Therefore, in view of the above, withdrawal of this rejection is respectfully requested.

Claims 40 to 41 have been rejected under 35 U.S.C. §102(e) as being anticipated by Relman et al. For the following reasons, this rejection is respectfully traversed.

In maintaining this rejection, the Examiner purports that column 2, lines 30 to 35 and claims 8 to 10 of Relman et al teach an N-terminal moiety consisting of an Fha N-terminal fragment. However, it should be clear that claim 40 of the present invention recites a cell culture in which the recombinant DNA encodes for an immunogenic translational fusion protein in which part of the precursor of Fha, which interacts with

heparin **is placed upstream** from a polypeptide which is heterologous with respect to Fha. The places in Relman et al, cited above by the Examiner, do not disclose such a translational fusion protein.

Furthermore, the only description in Relman et al that discloses a fusion protein is at column 9, lines 45 to 60. However, when Applicants presented arguments and evidence that the disclosed construct in Relman et al comprise an N-terminal moiety from MS2 and a C-terminal moiety corresponding to the fragment of Fha, the Examiner purports that Applicants "present arguments that are not recited in the claims." Applicants respectfully disagree with the Examiner's reasoning.

Claim 40 recites specifically that sequence (2) **is placed upstream** from sequence 1. Sequence 2 codes for at least part of the precursor of Fha, which comprises the interaction site with heparin. The terminology "placed upstream" is equivalent to sequence (2) being placed 5' to sequence (1). Therefore the N' terminal of the recombinant DNA construct of the present invention, as recited in claim 40 has 5' to 3', at least part of the precursor of Fha, which comprises the interaction site with heparin fused to the heterologous polypeptide.

It contrast the pEX34 plasmid decribed in Relman et al has the following 5' to 3' sequence:

λPL promoter: MS2 polymerase:Fha fragment.

This fact is evidenced by the disclosure of Strebel et al made of record in the last response. More specifically, the Examiner has not included any rebuttal arguments with respect to the references submitted in th last respons . It should be perfectly clear

from the teachings of Strebel et al that the vector pEX34 has an MS2 polymerase at the N-terminal and the appropriate nucleic acid sequence of interest is fused to this MS2 polymerase. This is evidenced by the following statement at page 983 of Strebel et al:

> The fusion protein expressed from the resulting construction pE34, thus **contains 98 N-terminal amino acids of the MS2 polymerase followed by** 25 amino acids which are encoded by an unused open reading frame of the virus (nucleotide positions 3848 to 3922) and the C-terminal part of P2 delimited by the *Ball* site (position 4463) and the *Eco*RI site (position 5149) (emphasis added)

Thus, the fusion protein produced in Relman et al has the Fha fragments downstream from the MS2 polymerase. In contrast the part of the Fha precursor recited in Claim 40 is upstream from the heterologous polypeptide.

As stated by the Federal Circuit in *Brown v. 3M,* 265 F3d 1349, 1351, 60 USPQ2d 1375 (Fed. Cir. 2001) *cert denied*, 122 S. Ct. 1436 (2002):

> To anticipate, every element and limitation to the claimed invention must be found in a single prior art reference, arranged as in the claim.

Since Relman et al does not disclose their recombinant DNA to produce a fusion protein in the correct order as recited in the present claims, this reference cannot be said to anticipate Claims 40 or 41.

Therefore, in view of the above, withdrawal of this rejection is respectfully requested.

Claims 1 and 34 have been rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement. For the following reasons, however, this rejection is respectfully traversed.

In rendering this rejection, the Examiner purports that new matter was added to these claims by deletion of the terminology "said sequence (2), when placed under the control of a promoter recognized by the cellular polymerases of *B. pertussis* and introduced into a *B. pertussis* cell culture is expressed in this culture and excreted into the culture medium of these cells or exposed at the surface of these cells, wherein said recombinant DNA when expressed produces highly immunogenic fusion proteins."

The amendment to claims 1 and 34 should render this rejection now moot. With respect to the amendment to claim 1, support can be found at least in claim 12 as originally filed. Thus, Applicants submit that no new matter has been added.

Therefore, in view of the above, withdrawal of this rejection is respectfully requested.

Claim 42 has been rejected under 35 U.S.C. §102 (e) as being anticipated by Relman et al. For the following reasons, this rejection is respectfully traversed.

Claim 42 depends from Claim 40. Therefore, the same reasons as set forth above in the rejection to claim 40 are incorporated by reference for this rejection; i.e., the fusion protein recombinant DNA of Relman et al is not arranged in the same order as that recited in Claim 40.

Thus, in view of the above, withdrawal of this rejection is respectfully requested.

LOCHT et al
Serial No. 08/765,287
January 23, 2004

From the foregoing, favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: Mary J. Wilson
Mary J. Wilson
Reg. No. 32,955

MJW:tat
1100 North Glebe Road, 8th Floor
Arlington, VA 22201-4714
Telephone: (703) 816-4000
Facsimile: (703) 816-4100